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ORIGINAL ARTICLE

An observational study of clinical recurrence in patients with interstitial lung disease related to the antisynthetase syndrome

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Abstract

Objective To describe the clinical characteristics and risk factors of clinical recurrence in interstitial lung disease related to antisynthetase syndrome (ARS-ILD).

Methods Patients diagnosed as ARS-ILD in Nanjing Drum Tower Hospital between January 2015 and November 2020 were retrospectively analyzed. Clinical information and treatment course were reviewed. The primary endpoint was the disease recurrence, and the secondary point was mortality. Univariate and multivariable Cox regression analyses were performed to identify risk factors for recurrence.

Results Totally, 132 patients with ARS-ILD received immunomodulation treatment from diagnosis. During follow-ups, sixty-nine patients showed recurrence, with a recurrency rate yielding 52.3%. The median duration from treatment initiation to recurrence was 11 (5–18) months. The median tapering course in the recurrence group was 8 (3–12.5) months, which was significantly shorter than the 16 (10–32) months in the no-recurrence group ($p < 0.001$). Fifty-eight patients experienced recurrence when the glucocorticoids (GC) dose dropped to 10 (9.375–15) mg/day. Twelve patients discontinued GC with a median treatment course of 11.5 (8–16.75) months, and 11 patients developed recurrence after discontinuing GC for 3 (1–4) months. Twelve patients died, with a mortality rate of 9.1%, and recurrence was not associated with increased mortality. The adjusted multivariate analysis showed that age, increased serum lactate dehydrogenase (LDH) level, relatively shorter tapering duration, and inappropriate GC discontinuation were associated with recurrence.

Conclusion Recurrence of ARS-ILD was common during medication intensity reduction. Age, LDH, medication tapering duration, and discontinuation were risk factors for recurrence. Further efforts to reduce recurrence should take into consideration of these factors.

Key Points

- *Recurrence is observed commonly with a recurrency rate 52.3% in patients with interstitial lung disease related to antisynthetase syndrome (ARS-ILD) when glucocorticoids (GC) tapering or discontinuation.*
- *Age, increased serum lactate dehydrogenase (LDH) level, medication tapering duration, and GC discontinuation were identified to be significantly associated with the recurrence of ARS-ILD.*

Keywords Antisynthetase syndrome · Glucocorticoids · Recurrence · Risk factor

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Introduction

Idiopathic inflammatory myopathies (IIMs) are a group of heterogeneous autoimmune diseases characterized by muscle inflammation and extra-muscular involvement. The main disease entities include polymyositis (PM), dermatomyositis (DM), antisynthetase syndrome (ARS), immune-mediated necrotizing myopathy, and sporadic inclusion body myositis [1]. ARS is defined by the presence of anti-aminoacyl tRNA

synthetase (anti-ARS) antibodies, plus one or more of the following symptoms: polyarthritis, interstitial lung disease (ILD), mechanic's hands, Raynaud phenomenon (RP), and fever [2–4]. Several anti-ARS antibodies have been identified: anti-Jo1, anti-EJ, anti-PL7, anti-PL12, anti-OJ, anti-KS, anti-Zo, and anti-Ha [5]. ILD is a severe manifestation with a prevalence rate ranging from 63 to 100% and is significantly associated with mortality [1, 6]. Glucocorticoid (GC) therapy was recommended as initial therapy in mild to moderate conditions. Pulse intravenous GC combined with immunosuppressive agents, such as tacrolimus and cyclosporine, was preferred in critical conditions. Biological agents, such as rituximab (RTX) and abatacept, are used in obstinate cases [7, 8].

Previous studies suggested that patients with ARS-ILD exhibit better response to immunomodulation compared to other ILD related to IIMs (IIM-ILD) subgroups. However, disease recurrence frequently occurs during medication tapering or discontinuation [9–12]. Studies showed that the recurrency rate in patients with ARS-ILD range from 30 to 50% [13–15]. Disease relapse is clinically significant because it may increase pneumonia attacks risk and impair the life quality [11, 14]. Sun et al. find that patients who experienced multiple recurrences within 1 year were more likely to go back for treatments than those with no recurrence [16]. The clinical characteristics of GC tapering or cessation in patients with ARS-ILD, and the risk factors for the recurrence of ARS-ILD, are unclear. We conducted this study to describe patient characteristics of recurrence during GC tapering or discontinuation, and to identify the risk factors for recurrence in patients with ARS-ILD.

Materials and methods

Subjects and data collection

Patients diagnosed with ARS-ILD in Nanjing Drum Tower Hospital from January 2015 to November 2020 were retrospectively analyzed. The diagnosis of ARS fulfilled the criteria proposed by Solomon et al. in 2011, which require two major or one major and two minor criteria in addition to the presence of an anti-ARS antibody [17]. The two major diagnostic criteria are the presence of ILD and myositis according to the criteria established by Bohan and Peter [18, 19]. The three minor criteria include arthritis, mechanic's hands, and RP. An ILD diagnosis was defined as respiratory symptoms and radiographic abnormalities on chest high-resolution computed tomography (HRCT). Patients with an identifiable cause of ILD, such as medication, environmental exposure, occupational exposure, and other connective tissue diseases related to ILD, were excluded. Patients who died within one month of admission were also excluded.

Demographic information included age of onset, sex, and smoking history. Clinical manifestations included fever, skin involvement (heliotrope rash, Gottron's sign, mechanic's hands, and RP), joint involvement (arthralgia and arthritis), and muscular involvement (myalgia and muscle weakness). Laboratory examinations included routine blood tests (white blood cell counts, lymphocyte counts, neutrophil counts, and hemoglobin levels), biochemical parameters (creatine kinase, kinase isoenzyme, lactate dehydrogenase, and C-reactive protein levels, and the erythrocyte sedimentation rate), and arterial blood gas (pO2 and pCO2). Baseline pulmonary function tests (PFTs), if available, were performed the percent predicted forced vital capacity (FVC% predicted) and the percent predicted diffusing capacity of the lung for carbon monoxide (DLCO% predicted).

Written informed consent was waived because of the retrospective design of this study. This study was approved by the Ethics Committee of Nanjing University Medical School Affiliated Drum Tower Hospital according to the policy (protocol number 2022–067-02, March 28, 2022).

Detection of serum autoantibodies

All patients were screened for myositis antibody profiles. Myositis serological tests (anti-Mi-2, anti-TIF1-γ, anti MDA5, anti NXP2, anti SAE1, anti-SRP, anti-Jo1, anti-EJ, anti-PL7, anti-PL12, anti-OJ, and anti Ro52) and anti-ARS antibodies (anti-Jo1, anti-EJ, anti-PL7, anti-PL12, and anti-OJ) were measured by a line immunoassay (Myositis Profile Euroline Blot test kit, Euroimmun, Lu¨beck, Germany) according to the manufacturer's protocol. The results were considered positive if the bands showed moderate to vigorous reactions.

Radiological analysis

All patients underwent chest HRCT at admission. Images were reviewed independently by two experienced radiologists blinded to the clinical information. HRCT findings were described as the nonspecific interstitial pneumonia (NSIP) pattern, organizing pneumonia (OP) pattern, NSIP/OP overlap pattern, and usual interstitial pneumonia (UIP) pattern based on the 2013 American Thoracic Society classification of idiopathic interstitial pneumonia guidelines [20].

Treatment and follow-up

Treatment information was recorded, including the initial GC dose, the current GC dose, and the treatment duration. The current GC dose was defined as the dose at the most recent visit, and GC tapering duration was the time from initial treatment to the current GC dose or recurrence. Disease recurrence was defined as a patient who fulfilled the

criteria for progression of ILD and required an increased GC dose on retreatment. Progression of ILD was defined as occurrence of 2 or more of the following: (1) deterioration in respiratory syndromes and/or PM/DM-related extrapulmonary symptoms; (2) an increase in ILD-related abnormalities on chest HRCT; and (3) an absolute decrease in FVC% > 5% predicted or an absolute decrease in DLCO% > 10% predicted within 1 year of follow-up [21]. The GC dose and the time from treatment to recurrence were recorded at relapse. All relapsed patients received retreatment, and the increased dose of GC on retreatment had be recorded. All patients were informed to visit every 3 to 6 months to evaluate the treatment response. Assessment of the response to treatment included physical examinations, chest radiographs, and PFTs.

Statistical analysis

Dichotomous variables were expressed as percentages and absolute frequencies, and continuous variables were expressed as the means and standard deviations (SD) or medians and interquartile ranges (IQR). Pairwise comparisons for categorical variables between groups were made using the chi-square test or Fisher's exact test. The *t* test or the Mann−Whitney *U* test was used to compare continuous variables. The Cox proportional hazards model was used for univariate and multivariate survival analyses to calculate the hazard ratios (HR) and the corresponding 95% confidence intervals (CI). All statistical analyses were performed using SPSS V.21.0, Microsoft Excel 2019, and GraphPad Prism software version 8.0.2. The results were considered significant when *P* values were < 0.05.

Results

Demographic, clinical, and laboratory features

The study included 200 patients diagnosed with ARS-ILD. After excluding 68 patients for incomplete data, 132 patients who received immunomodulation treatment were enrolled. The median (IQR) duration from symptom onset to diagnosis was 2 (1–8.75) months. There were 85 (85/132, 64.4%) females and 47 (47/132, 35.6%) males, with a mean age of 55.3 ± 11.3 years. Twenty-two (22/132, 16.7%) patients were current or former smokers. The most frequent anti-ARS antibody was anti-Jo1, which was detected in 60 (60/132, 45.5%) patients, followed by anti-EJ in 32 (32/132, 24.2%), anti-PL7 in 20 (20/132, 15.2%), anti-PL12 in 17 (17/132, 12.9%), and anti-OJ in 3 (3/132, 2.3%). The most common extrapulmonary manifestation was mechanic's hand (40/132, 30.3%), followed by fever (32/132, 24.2%), arthritis/arthralgia (31/132, 23.5%), Gottron's sign (29/132, 22.0%), myalgia/muscle weakness (17/132, 12.9%), heliotrope rash (13/132, 9.8%), and RP (3/132, 2.3%).

One hundred patients underwent baseline PFTs. The mean FVC % predicted was 61.77 ± 15.64%, and the mean DLCO% predicted was 51.80 ± 17.75%. The most common HRCT pattern was NSIP (69/132, 52.3%), followed by OP (34/132, 25.8%) and NSIP/OP (23/132, 17.4%). Six (6/132, 4.5%) patients had the UIP pattern.

Treatment information

All patients were initially treated with GC at a median dosage of 40 (30–40) mg/day. Among them, 20 (20/132, 15.2%) patients received GC as monotherapy, whereas 112 (112/132, 84.8%) patients received GC combined with immunosuppressant agents, including cyclophosphamide in 43 (43/132, 32.6%) patients, hydroxychloroquine in 21 (21/132, 15.9%) patients, tacrolimus in 22 (22/132, 16.7%) patients, cyclosporine in 36 (36/132, 27.3%) patients, and mycophenolate in 4 (4/132, 3.0%) patients (Table 1).

Sixty-three (63/132, 47.7%) patients remained in remission or remained stable with a median follow-up time of 29 (14–43) months. The median initial GC dose was 40 (30–40) mg/day, and the current GC dose was 10 (5–10) mg/day. The median GC tapering duration was 16 (10–32) months.

Sixty-nine patients experienced recurrence during medication reduction or withdrawal, with a recurrency rate of 52.3%. Sixty-one (61/69, 88.4%) patients showed HRCT deterioration, 1 (1/69, 1.4%) patients had decreases in PFTs, and 7 (7/69, 10.1%) patients showed deterioration both in HRCT and PFTs. Myositis-related symptoms simultaneously recurred in twenty (20/69, 29.0%) patients (Table 2). The median time from initiation of treatment to recurrence was 11 (5–18) months. The median current GC dose was 10 (5–15) mg/day at disease recurrence. The median GC tapering duration was 8 (3–12.5) months. The current GC dose between the recurrence and no-recurrence groups showed no significant difference, and the GC tapering duration distributions are shown in Fig. 1. The GC tapering duration was significantly shorter in the recurrence group than in the no-recurrence group ($p < 0.001$). Among the patients' recurrency rate in anti-ARS antibodies subtypes, patients with anti-Jo1 had the most population (38/69, 55.1%), followed by anti-EJ (14/69, 20.3%), anti-PL7 (9/69, 13.0%), anti-PL12 (7/69, 10.1%), and anti-OJ (1/69, 1.4%). As shown in Table 1, the disease return rate in anti-Jo1 patients was higher than those in non-Jo1 patients (63.3% versus 43.1%; $P = 0.02$).

Twelve (12/132, 9.1%) patients discontinued GC, including 10 with poor medication adherence. The duration of treatment among those patients was 11.5 (8–16.75) months. Except for one patient who discontinued the medication successfully, other patients suffer from recurrence in

Table 1 Comparison of clinical characteristics between the recurrence and no-recurrence groups of patients with ARS-ILD

	ARS-ILD	Recurrence	No-recurrence	*P* value
No	132	69	63	/
Age at onset, years	55.3 ± 11.3	55.8 ± 11.3	54.7 ± 11.3	0.568
Male/female	47/85	21/48	26/37	0.194
Ever-smoker	22 (16.7)	10 (14.5)	12 (19.0)	0.483
Disease duration, month	2 (1–8.75)	2 (1–6)	3 (1–12)	0.055
Mortality	12 (9.1)	9 (13.0)	3 (4.8)	0.098
Clinical characteristic				
Fever	32 (24.2)	20 (29.0)	12 (19.0)	0.183
Heliotrope rash	13 (9.8)	7 (10.1)	6 (9.5)	0.905
Gottron's sign	29 (22.0)	12 (17.4)	17 (27.0)	0.184
Myalgia/ Muscle weakness	17 (12.9)	10 (14.5)	7 (11.1)	0.562
Arthritis/arthralgia	31 (23.5)	19 (27.5)	12 (19.0)	0.250
Mechanic's hand	40 (30.3)	19 (27.5)	21 (33.3)	0.469
Raynaud phenomenon	3 (2.3)	2 (2.9)	1 (1.6)	0.999
Laboratory findings				
WBC, $\times 10^9$/L	8.49 ± 3.78	8.61 ± 4.06	8.37 ± 3.47	0.721
N, %	72.10 ± 12.30	72.06 ± 13.36	72.13 ± 11.16	0.976
L, %	19.99 ± 9.35	19.69 ± 10.06	20.31 ± 8.60	0.705
HB, g/L	132.44 ± 15.73	131.94 ± 14.61	132.97 ± 16.96	0.710
CK, U/L	163.72 ± 314.09	161.28 ± 281.39	166.44 ± 349.24	0.926
CK MB, U/L	14.95 ± 11.17	14.96 ± 11.28	14.93 ± 11.15	0.992
LDH, U/L	307.98 ± 133.67	325.44 ± 146.30	288.86 ± 116.47	0.117
CRP, mg/L	12.87 ± 22.83	13.19 ± 23.71	12.52 ± 22.00	0.866
ESR, mm/h	25.90 ± 19.21	24.83 ± 20.75	27.03 ± 17.56	0.523
PCO2, mmHg	37.38 ± 5.01	37.48 ± 4.69	37.26 ± 5.43	0.841
PO2, mmHg	81.38 ± 20.77	77.58 ± 19.90	85.81 ± 21.11	0.059
Baseline PFTs (recurrence = 47; no-recurrence = 53)				
FVC predicted, %	61.77 ± 15.64	60.78 ± 15.43	62.64 ± 15.91	0.554
DLco predicted, %	51.80 ± 17.75	50.11 ± 17.25	53.27 ± 18.21	0.390
HRCT pattern				
NSIP	69 (52.3)	34 (49.3)	35 (55.6)	0.471
OP	34 (25.8)	21 (30.4)	13 (20.6)	0.198
NSIP/OP	23 (17.4)	13 (18.8)	10 (15.9)	0.653
UIP	6 (4.5)	1 (1.4)	5 (7.9)	0.084
Presence of antibodies				
ANA	82 (62.1)	42 (60.9)	40 (63.5)	0.756
Ro-52	105 (79.5)	52 (75.4)	53 (84.1)	0.212
Jo1	60 (45.5)	38 (55.1)	22 (34.9)	0.020
EJ	32 (24.2)	14 (20.3)	18 (28.6)	0.267
PL7	20 (15.2)	9 (13.0)	11 (17.5)	0.480
PL12	17 (12.9)	7 (10.1)	10 (15.9)	0.326
OJ	3 (2.3)	1 (1.4)	2 (3.2)	0.606
Treatment				
GC tapering	119 (90.2)	58 (84.1)	61 (96.8)	/
GC discontinuation	12 (9.1)	11 (15.9)	1 (1.6)	0.004
Initial GC dose, mg/day	40 (30–40)	40 (30–40)	40 (30–40)	0.917
GC tapering duration, months	11 (6–19.75)	8 (3–12.5)	16 (10–32)	< 0.001
Current GC dose, mg/day	10 (5–15)	10 (5–15)	10 (5–10)	0.560
GC monotherapy	20 (15.2)	11 (15.9)	9 (14.3)	0.791
GC + Cyclophosphamide	43 (32.6)	19 (27.5)	24 (38.1)	0.196
GC + Hydroxychloroquine	21 (15.9)	10 (14.5)	11 (17.5)	0.642

Table 1 (continued)

	ARS-ILD	Recurrence	No-recurrence	*P* value
GC + Tacrolimus	22 (16.7)	13 (18.8)	9 (14.3)	0.483
GC + Cyclosporine	36 (27.3)	20 (29.0)	16 (25.4)	0.644
GC + Mycophenolate	4 (3.0)	2 (2.9)	2 (3.2)	0.999

Data are presented as *n* (%), mean ± SD, or median (IQR)

WBC white blood cell count, *N* neutrophil count, *L* lymphocyte count, *HB* hemoglobin, *CK* creatine kinase, *CK* MB kinase isoenzyme, *LDH* lactate dehydrogenase, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *PFTs* pulmonary function tests, *FVC* forced vital capacity, *DLCO* diffusion capacity for carbon monoxide of the lung, *HRCT* high-resolution computed tomography, *NSIP* nonspecific interstitial pneumonia, *OP* organizing pneumonia, *UIP* usual interstitial pneumonia, *ANA* anti-nuclear antibody, *GC* glucocorticoids

Table 2 Recurrence group characteristics for GC tapering and discontinuation

	Recurrence group	GC tapering	GC discontinuation
No	69	58	11
Myositis recurrence	20 (29.0)	14 (24.1)	6 (54.5)
HRCT deterioration	61 (88.4)	50 (86.2)	11 (100)
Decreased PFTs	1 (1.4)	1 (1.7)	0
Both HRCT and PFTs	7 (10.1)	7 (12.1)	0
Mortality	9 (13.0)	5 (8.6)	4 (36.4)
Initial GC dose, mg/day	40 (30–40)	40 (30–40)	30 (20–40)
Current GC dose, mg/day	10 (5–15)	10 (9.375–15)	0
GC dose on retreatment, mg/day	30 (17.5–30)	30 (20–30)	30 (15–30)
Time from initiation treatment to recurrence, months	11 (5–18)	9.5 (4–16.25)	14 (10–19)
GC tapering duration, months	8 (3–12.5)	6.5 (2.75–11.25)	11 (8–18)
Duration of current dose/discontinuation, months	2 (1–4)	2 (1–4.25)	3 (1–4)

Data are presented as *n* (%), or median (IQR)

HRCT high-resolution computed tomography, *PFTs* pulmonary function tests, *GC* glucocorticoids

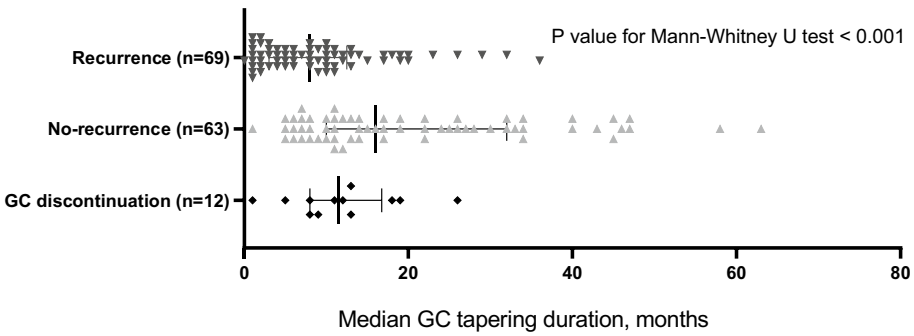

Fig. 1 The median GC tapering duration of recurrence and no-recurrence groups

3 (1–4) months, 5 in 1 month, 3 in 3 months, 1 in 4 months, and 2 in 6 months. The medium period from the initial dose to readmission was 14 (10–19) months. All relapsed patients started reinduction with a median of 30 (15–30) mg/day GC. All clinical performance of patients improved in the follow-ups (Table 2).

Survival analysis and risk factors for the recurrence of ARS-ILD

Twelve of 132 (12/132, 9.1%) patients died with a median follow-up period of 16 (12.25–20.50) months. The main causes of death were infection and acute exacerbation of

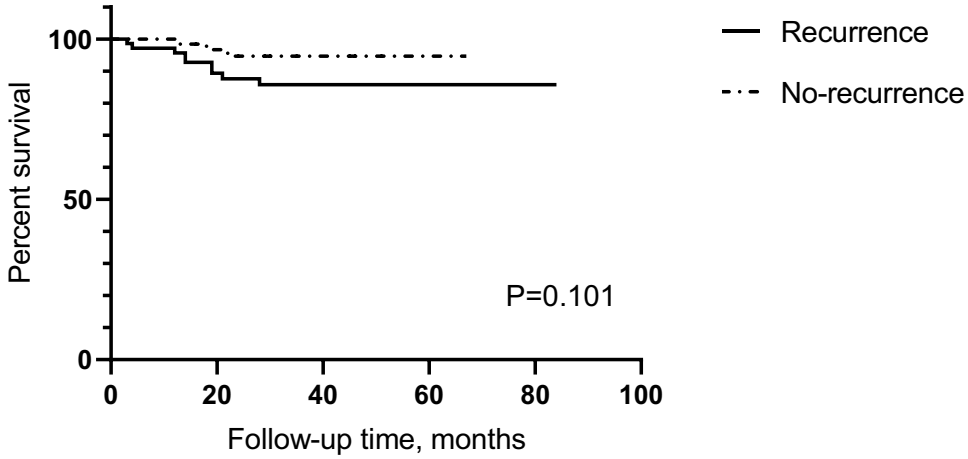

Fig. 2 Survival curves in patients with ARS-ILD between recurrence and no-recurrence group

respiratory symptoms. Disease recurrence occurred in nine patients, and the median duration from recurrence to death was 10 (1.5–14.5) months. The mortality rate between the recurrence and no-recurrence groups showed no significant difference, and the recurrent ARS-ILD did not contribute to the increased mortality (Fig. 2, $P = 0.101$).

We conducted a univariate analysis using the Cox proportional hazard model (Table 3). Increased serum LDH level (HR = 1.002, 95% CI 1.000–1.004, $P = 0.013$), shorter GC tapering duration (HR = 0.837, 95% CI 0.798–0.879, $P < 0.001$), and inappropriate GC discontinuation (HR = 2.130, 95% CI 1.112–4.079, $P = 0.023$) were associated with recurrence of ARS-ILD in univariate analysis. After adjusting for sex, age, and anti-ARS antibodies, multivariate analysis showed that older age (HR = 1.029, 95% CI 1.003–1.056, $P = 0.030$), increased serum LDH level (HR = 1.002, 95% CI 1.000–1.003, $P = 0.023$), GC tapering duration (HR = 0.813, 95% CI 0.770–0.858, $P < 0.001$), and GC discontinuation (HR = 2.551, 95% CI 1.294–5.029, $P = 0.007$) were independent predictors for recurrence of ARS-ILD.

Discussion

This observational study showed that clinical relapse in ARS-ILD was common when GC dose was reduced or discontinued, with a recurrency rate of 52.3%. The prevalence of disease recurrence was higher in individuals with anti-Jo1. The GC tapering duration in the recurrence group was significantly shorter than that in the no-recurrence group. Age, increased serum LDH level, GC tapering duration, and inappropriate GC discontinuation were associated with recurrence of ARS-ILD. These factors need to be taken into account when treating patients with ARS-ILD.

Previous studies have explored the potential connections between recurrence and anti-ARS antibodies [16, 22]. Patients with anti-Jo1 had higher possibilities to experience relapse than those with non-Jo1 [23]. However, Zhang et al. found the highest recurrency rate in anti-EJ patients (52.9%) [24]. Sun et al. discovered that anti-PL7 was significantly correlated with rapidly progressive ILD, and patients with anti-PL7 more frequently exhibited deterioration in respiratory syndromes compared to other anti-ARS antibodies [16]. Marie et al. found that patients with anti-Jo1 have a higher recurrency rate than patients with anti-PL7/PL12 (65.9% versus 19.4%) [23]. Patients with anti-Jo1 who initially displayed more severe muscular weakness were more likely to experience recurrence [22]. A high initial level of LDH in patients with anti-Jo1 may indicate more pronounced muscle involvement, possibly because LDH is extensively expressed in skeletal muscles and released following tissue injury [25]. Meanwhile, in this study, serum LDH was closely related to recurrence in patients with anti-Jo1. When treating patients with ARS-ILD, we may pay attention to the dynamic variations in serum LDH level.

GC is widely employed in newly diagnosed and relapsed patients with ARS-ILD [9, 10, 22, 26]. Currently, there are no uniform standard regimens for the dose and duration of GC therapy. The maintenance GC doses used in previous studies ranged from 5 to 20 mg/day [11, 27, 28]. According to a study of 12 patients with anti-Jo1, relapse occurred in five patients when the GC dose decreased to 7.5 mg/day, and GC discontinuation was significantly associated with recurrence [28]. Marie and colleagues found that recurrence occurred in more than 90% of patients receiving GC at a dosage of 20 mg/day [27]. Another study was consistent with this finding; there were considerably more patients who had GC dose halved in the recurrence group than in the no-recurrence group (80% versus 38%) at the eighth week, suggesting that the rapid reduction in GC dose have a connection with recurrence of ARS-ILD [11]. However, the correlation between the rapid decrease in GC dose with recurrence remains to be further investigated. Depending on the

Table 3 Cox regression analysis of characteristics associated with the recurrence of ARS-ILD

Variable	Univariable		*P* value	Multivariable		*P* value
	HR	95% CI		HR	95% CI	
Age, years	1.018	0.997–1.039	0.093	1.029	1.003–1.056	0.030
Sex						
Male	Ref			Ref		
Female	1.174	0.702–1.964	0.541	1.407	0.815–2.428	0.220
Duration, months	0.998	0.982–1.015	0.826			
Ever-smoker	1.048	0.534–2.057	0.892			
Laboratory findings						
WBC (×109/L)	1.011	0.946–1.080	0.755			
ESR, mm/h	0.996	0.982–1.010	0.555			
LDH, U/L	1.002	1.000–1.004	0.013	1.002	1.000–1.003	0.023
Clinical characteristic						
Fever	1.425	0.846-2.398	0.183			
Heliotrope rash	0.863	0.395–1.886	0.711			
Gottron's sign	0.674	0.362–1.257	0.215			
Myalgia/ Muscle weakness	1.510	0.771–2.957	0.229			
Arthritis/arthralgia	1.376	0.811–2.334	0.237			
Mechanic's hand	0.773	0.456–1.311	0.340			
Raynaud phenomenon	0.976	0.239–3.988	0.973			
Anti-ARS antibodies						
Jo1	1.521	0.945–2.446	0.084	5.068	0.681–37.711	0.113
EJ	0.699	0.389–1.258	0.233	3.849	0.491–30.161	0.199
PL7	0.873	0.433–1.762	0.705	2.338	0.290–18.838	0.425
PL12	0.823	0.377–1.800	0.626	1.309	0.155–11.037	0.805
OJ	0.738	0.102–5.339	0.764			
ANA	0.926	0.571–1.502	0.755			
Ro-52	0.760	0.439–1.315	0.327			
HRCT pattern						
NSIP	0.847	0.528–1.358	0.490			
OP	1.346	0.806–2.250	0.256			
NSIP/OP	1.080	0.589–1.978	0.804			
UIP	0.324	0.045–2.334	0.263			
Therapy						
Initial GC dose	0.989	0.955–1.024	0.534			
GC tapering duration	0.837	0.798–0.879	<0.001	0.813	0.770–0.858	<0.001
GC monotherapy	1.293	0.678–2.465	0.436			
Combination therapy	0.774	0.406–1.475	0.436			
GC discontinuation	2.130	1.112–4.079	0.023	2.551	1.294–5.029	0.007

WBC white blood cell count, *ESR* erythrocyte sedimentation rate, *LDH* lactate dehydrogenase, *ANA* antinuclear antibody, *HRCT* high-resolution computed tomography, *NSIP* nonspecific interstitial pneumonia, *OP* organizing pneumonia, *UIP* usual interstitial pneumonia, *GC* glucocorticoids

severity of the disease, high doses of GC were recommended for recurrence cases [29]. In a study of 51 patients with anti-EJ related to ILD, 11 patients relapsed at the GC dose of 11.6 mg/day with a mean follow-up duration of 12 months and were given higher GC at the level of 28.3 mg/day [9]. Evidence-based protocols for GC reduction and discontinuation are required to guide clinicians to treat patients with ARS-ILD.

Immunosuppressants are recommended for patients who are resistant to GC or who cannot tolerate its negative effects [22, 30]. GC combined with immunosuppressant agents was associated with fewer recurrences than GC monotherapy, and starting immunosuppressants as the first step in therapy could have a steroid-sparing effect on patients [11, 22, 31]. Calcineurin inhibitors (tacrolimus and cyclosporine) are widely used to reduce the disease flare [11, 14, 32]. Takei

et al. found that the recurrency rate in patients treated with tacrolimus was significantly lower than that in those treated with cyclosporine (30.4% versus 76.7%), and calcineurin inhibitor discontinuation was a risk factor for recurrence of ARS-ILD [15]. Cavagna and colleagues discovered that cyclosporine had a significant steroid-sparing effect (GC dose decreased from 25 to 2.5 mg/day) on patients with recurrence within 1 year, and cyclosporine discontinuation was associated with disease recurrence [33]. RTX was performed as an alternative therapy for patients with steroid-refractory disease [16, 34]. According to the retrospective study by Andersson et al., seven patients with ARS-ILD developed an average of 30% in FVC% and DLCO% predicted after receiving RTX during 1 year of follow-up [34]. Patients with ARS-ILD achieved a significant steroid-sparing effect (GC dose decreased from 18 to 12 mg/day) after receiving 1 year of RTX treatment [34]. More clinical trials are needed to compare the efficacy of different immunosuppressants.

PFTs and HRCT are important indicators to assess the management of ARS-ILD [35]. Gonzalez-Perez and colleagues found that PFTs improvements occurred in 67% of patients with ARS-ILD within the first 6 months after initiating treatment [36]. However, a significant decline could be observed at regular PFTs, suggesting a correlation between PFTs and the extent of ILD [36, 37]. Maho et al. identified a reduced baseline FVC% as a risk factor for recurrence of IIM-ILD within 52 weeks [11]. In a study of 49 patients with IIM-ILD, FVC% below 80% was an adverse factor for recurrence [38]. By comparing the distinction in HRCT patterns of ARS-ILD, Liu et al. discovered that the recurrence group experienced considerably more NSIP patterns compared to the no-recurrence group (81.8% versus 45.5%) [9]. However, another study showed that patients with the UIP were more prone to developing recurrence, possibly because patients with the NSIP and OP were more sensitive to immunomodulation therapy [39, 40]. Several randomized trials have assessed the efficacy of antifibrotic therapy in IIM-ILD [41, 42]. In a study of 19 patients with IIM-ILD (disease duration from 3 to 6 months), the survival rate was significantly higher in patients treated with pirfenidone than in those treated with conventional immunomodulation [42]. Liang et al. retrospectively analyzed 151 patients with IIM-ILD from January 2018 to March 2020, and found that patients who received both nintedanib and immunosuppressants had a better prognosis than those treated with immunosuppressants alone [43]. In our study, three patients received pirfenidone or nintedanib for antifibrotic therapy, and no-recurrence occurred. The value of antifibrotic in the recurrence of ARS-ILD remains to be explored.

Our study has a few limitations. First, this was a single-center, retrospective study, and biases were unavoidable. Second, the sample size limited the ability to evaluate the association between immunomodulation treatment and the recurrence of ARS-ILD.

In conclusion, our study revealed that the recurrency rate in patients with ARS-ILD was 52.3%. Age, increased serum LDH level, GC tapering duration and inappropriate GC discontinuation were associated with the recurrence of ARS-ILD. To determine the appropriate GC dosages and durations to reduce the recurrence risk, further prospective and randomized controlled trials are required.

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Declarations

Ethics approval This study was approved by the Ethics Committee of Nanjing University Medical School Affiliated Drum Tower Hospital according to the policy (protocol number 2022–067-02, March 28, 2022).

Disclosures None.

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